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66. (Twice Amended) An article of manufacture adapted for use in an immunoassay for antibodies to an human immunodeficiency virus (HIV) comprising a solid support having bound thereto a synthetic [HIV] polypeptide comprising at least a portion of an envelope (*env*) antigen comprising an immunogenic amino acid sequence of the *env* [at least an antigenic portion of the envelope (env)] domain of said HIV, wherein said synthetic polypeptide is prepared by chemical synthesis.

**REMARKS**

The Present Invention

The present invention is predicated on the identification of a certain domain of the human immunodeficiency virus (HIV), as well as the nucleic acid sequence of the gene that encodes that domain. Applicants were the first to uncover this necessary information and, further, were the first to recognize the use of this information for the chemical synthesis of polypeptides of the identified domain.

In particular, the present invention is directed to an immunoassay for the detection of HIV in a clinical sample using synthetic HIV polypeptides derived from the envelope (*env*) domain. Embodiments of the present invention include

an article of manufacture by which the immunoassay is performed.

The Claims

Claims 60, 61 and 66 were amended to increase their clarity and distinctiveness by including further description of the synthetic polypeptide used in the context of the present invention. These amendments are supported in the specification by the recitation: "Based on the nucleotide sequences, synthetic peptides may also be prepared" (specification at p. 5, ll. 3-4), as interpreted in terms of the conventional knowledge used by one of ordinary skill in the art to interpret them, wherein the conventional knowledge predates October 31, 1984. See In re Chilowsky, 229 F.2d 457, 460, 108 U.S.P.Q. 321, 324 (C.C.P.A. 1956), quoted in In re Howarth, 654 F.2d 103, 106, 210 U.S.P.Q. 689, 692 (C.C.P.A. 1981) ("It is well settled that the disclosure of an application embraces not only what is expressly set forth in words or drawings, but what would be understood by persons skilled in the art."); also see Hybritech Incorporated v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81 (Fed. Cir. 1986). The inclusion of the modifier "immunogenic" in claims 60, 61, and 66 is supported in the specification of the present application as well as those of

its priority applications, e.g., in Serial No. 667,501, at page 14, lines 17-21. Accordingly, no new matter has been added by way of the recited amendments.

Claims 60-66 are pending in the present application. Claims 60-65 are directed to a method of detecting antibodies to a human immunodeficiency virus (HIV). Claim 66 is directed to an article of manufacture adapted for use in an immunoassay for antibodies to HIV.

The Office Action

The Office Action of March 31, 1995, rejected the claims of the present application as follows:

(1) claims 60-66 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification is allegedly nonenabling;

(2) claims 60-66 stand rejected under 35 U.S.C. § 112, second paragraph, because the claims are allegedly indefinite; and

(3) claims 60-66 stand rejected under 35 U.S.C. § 102(b) or 102(e) as allegedly being anticipated by Chang et al. (U.S. Patent 4,774,175) or Cosand (U.S. Patent 4,629,-783).

Discussion Of The Nonenablement Rejection

Claims 60-66 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification is allegedly nonenabling. Applicants respectfully traverse this formal rejection in view of the words of the specification as understood by one of ordinary skill in the art, as discussed hereinbelow.

One of ordinary skill is presumed to have command of conventional knowledge of the relevant art at the relevant time and to have the ability to locate additional information from popular or usual sources of information, such as textbooks, mainstream journals, etc. Conventional knowledge forms the context in which a specification is properly read. Hybritech, supra; Howarth, supra. Only once the context is identified can one properly assess enablement of a specification. As fully discussed in the Hybritech case, enablement is a legal determination of whether a patent enables one of ordinary skill in the art to make and use the claimed invention. Enablement is not precluded even if some experimentation is needed. Indeed, even "a considerable amount of experimentation is permissible if it is merely routine." In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). In fact, because "a patent need not teach, and preferably omits, what is well known in the art,"

enablement under the statute is satisfied so long as any non-conventional information required to make and practice the invention is disclosed. Hybritech, 802 F.2d at 1384, 231 U.S.P.Q. at 98.

Applicants respectfully submit that the pending claims are enabled not only by the present application, but also by its earliest priority application, i.e., Ser. No. 667,501 (filed October 31, 1984; "the '501 application"). Accordingly, conventional knowledge in the possession of one of ordinary skill in the relevant art that predates October 31, 1984, forms part of the support for the pending claims, in addition to the words of the specification and any information that is incorporated by reference therein. See Howarth, supra. Examples of such knowledge were offered in the Amendment dated December 22, 1994 ("the December 22nd Amendment"). They are readily available, well-known references that predate the filing date of the '501 application. Those references included:

1. Maniatis et al., Molecular Cloning: A Laboratory Manual (Cold Spring Harbor, NY, 1982) (a practical manual of molecular cloning and related techniques).

2. Geysen et al.,[1] Proc. Natl. Acad. Sci. USA, 81, 3998-4002 (July, 1984) (discloses a method for identification of epitopes).

[1] Geysen et al. was mistakenly identified at page 9 of the December 22nd Amendment as having been published in the journal Biochemistry. As clearly marked on the copy of this reference

3. Merrifield, J. Am. Chem. Soc., 85, 2149-2154 (1963) (discloses a method of chemical synthesis of polypeptides).

4. Spatola, in Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, Vol. 7, pp. 267-357 (B. Weinstein, ed., Decker, NY, 1983) (discloses methods of chemical synthesis of polypeptides).

5. Lehninger, Biochemistry (Worth Publishers, NY, 1970) (standard biochemistry text, discloses *inter alia* methods by which proteins are characterized and isolated).

In addition, one may add the standard immunology text book by Klein (Immunology (John Wiley & Sons, NY, 1982)) particularly at pages 397-407, which presents a formal as well as a practical treatment of various immunological techniques that are usefully applied when experimenting to identify useful antigenic portions of a polypeptide, such as the *env* polypeptide.

Against at least this backdrop of conventional knowledge should one consider the question of enablement of the pending claims. The pending claims each include recitation that the synthetic polypeptide used in the context of the present invention is prepared by chemical synthesis. That such a synthetic peptide was in the mind of applicants is clearly indicated by the last line of the

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that was filed with the December 22nd Amendment, Geysen et al. was in fact published in the Proceedings of the National Academy of Science.

Summary Of The Invention at page 3 of the '501 specification. Therein, applicants stated that "[b]ased on the nucleotide sequences, synthetic peptides may also be prepared." From the preceding statements in the Summary in addition to those of the Description Of The Specific Embodiments section, one of ordinary skill would readily comprehend that the synthetic polypeptides are to be used in immunoassays and vaccines, for example, just as recombinant proteins are to be used in other inventive embodiments disclosed in the present and priority applications.

The remainder of the '501 specification carefully presents the experiments by which applicants obtained, i.e., isolated, sequenced, and identified the various domains of HIV. On the strength of the conventional knowledge, as exemplified hereinabove, one of ordinary skill in the art can make and use the claimed invention by simply reading and applying the sequence information in Figure 4 coupled to the instruction included in the Summary for preparing synthetic peptides, using chemical means well known in the art.

The Office Action recites at page 4, lines 14-25, that the data presented in the specification relating to the identity of antigens expressed in COS cells are flawed. Such an opinion is, of course, irrelevant if applicants are correct that this explanation does exemplify a recombinant

*env* immunoassay. Section 112 does not require provision of a working example or proof of the theory underlying an invention for satisfaction of the statute.

In any event, the data presented in the priority and present applications are not flawed. Submitted herewith is the Expert Report of Professor B. Matija Peterlin, which was presented in the current litigation of Chiron Corporation v. Abbott Laboratories, C 93 4380 MHP (N.D. Calif.). As stated therein at page 2, lines 8-10, "reports by many investigators confirmed that [staining of transfected COS cells with an AIDS antiserum] was due to the expression of Env." Contrary affidavits by Abbott will be submitted presently in a Supplemental Information Disclosure Statement.

The Office Action states that undue experimentation would be required to determine which synthetic HIV polypeptide would function in immunoassays for the presence of anti-HIV antibodies, and that the disclosure provides information relating to the identification of immunogenic portions of the envelope (*env*) domain of HIV with respect to recombinantly expressed antigens only. The Office Action further contends that the disclosure does not enable production of HIV polypeptides that are not produced by recombinant means. The Office Action also discounts the

effect of the Geysen et al. reference because of the following contentions:

(1) there is no guidance in the instant or parent specifications that leads to Geysen et al., or to methods of determining antigenic peptides;

(2) it cannot be concluded solely from Geysen's teachings that the Geysen procedure would work for proteins not disclosed in Geysen, such as an envelope domain-encoded membrane glycoprotein;

(3) Geysen et al. recite that the antigenic response of any one individual is idiosyncratic and thus a portion of an HIV polypeptide is less effective than the entire protein; and

(4) Geysen et al. do not address how to produce synthetic peptides that possess conformational, as opposed to linear, epitopes, or how to produce large peptides, or, if produced, how to properly fold such peptides into a native conformation.

Applicants respectfully submit that only routine experimentation would be required to determine which portion of an HIV polypeptide would function in the immunoassays of the present invention. As of the filing date of the '501 application, the earliest priority application of the present application, one of ordinary skill in the relevant

art routinely could have constructed peptide fragments of an HIV polypeptide using nucleic acid and/or protein chemical methods and test such fragments for immunogenicity generally, or, more particularly, utility in an immunoassay of the present invention. The conventional knowledge that the routineer would have used could have been found in many places, including the aforementioned Klein Immunology and Lehninger Biochemistry.

Applicants further note that the identification of functional fragments of a given antigen as of the earliest priority date of the present application was purely a routine matter. For example, antigenic polypeptide fragments can be predicted from a hydrophilicity analysis of the amino acid sequence. This technique has been known for many years and was recently reviewed by Hopp (Peptides Research, 6, 183-190 (1993)), who noted that the original publication of the hydrophilicity method for locating antigenic determinants dates to 1981. Even computer programs have been established for determining relative hydrophilicity of the amino acids of a given polypeptide as of before the priority date. See Hopp et al., Proc. Natl. Acad. Sci. USA, 78, 3824-3828 (1981); Hopp et al., Molecular Immunology, 20, 483-489 (1983); Kyte et al., J. Mol. Bio., 157, 105-132 (1982); and EP-A-0154902.

Hopp et al. (1983) describe the prediction of the antigenic regions of the hepatitis B surface antigen (HBsAg) and twelve other test antigens (p. 483, col. 1). The authors note that their computer program correctly predicted the major antigenic determinant of HBsAg. Moreover, in connection with influenza hemagglutinin, the program was able to predict eight antigenic sites of which five were confirmed to be actual antigenic epitopes in the literature (p. 487 and Table 1).

To emphasize the routine nature of this type of computer epitope mapping, provided herewith is a copy of the Declaration of Dr. Sanchez-Pescador (one of the named inventors), filed in connection with the aforementioned Chiron v. Abbott litigation. Dr. Sanchez-Pescador's declaration includes an exhibit of a hydrophobicity map (equivalent to a relative hydrophilicity map) of the envelope region of ARV2 generated by him on October 3, 1984 (before the earliest claimed priority date). Once the genomic nucleotide sequence was known and an amino acid sequence could be inferred, it was a routine matter to generate a hydrophobicity plot, as indeed Dr. Sanchez-Pescador duly did. From this, predictions of antigenic epitopes could be made and, by chemical synthesis and assay against sera from HIV infected patients, immunologically

active fragments were selected. The information in the hydrophobicity plot is directly derivable from the specifications of the present or priority applications (i.e., from Figure 4, which provides the amino acid sequence for entry in the computer program; and which is identical in the '501 application, Ser. No. 696,534 (filed January 30, 1985; "the '534 application"), and the present application).

Neither is the Office Action's criticism valid that the specification only provides an enabling disclosure as to recombinantly expressed antigens. Once the nucleic acid sequence for the envelope domain genes of interest was known, as disclosed in the instant and parent applications, one of ordinary skill could have synthesized portions of an HIV polypeptide by chemical means and screened such portions for immunogenic response and/or utility in an immunodiagnostic test using the conventional methods known at the time.

For example, large peptides were obtainable by protein chemistry means prior to 1984, as evidenced by a 1970 biochemistry textbook that reports the then recent accomplishment of the "complete automated synthesis of the polypeptide chain of bovine pancreatic ribonuclease (124 residues), the first protein to be synthesized in the laboratory from its amino acid components." Lehninger,

Biochemistry, p. 104. Clearly, such large polypeptides of variant sequence could be combined in various combinations to construct yet larger polypeptides, to the extent of the equivalent of the envelope antigens, using only conventional protein synthesis technology.

Accordingly, the claims are enabled with respect to production of HIV polypeptides by non-recombinant means. Therefore, the method disclosed in the present specification at page 125, line 15, to page 137, line 2, albeit related with respect to recombinant polypeptides, are applicable for polypeptides generated by chemical synthetic means as well. Moreover, even the '501 application fully enables the pending claims in view of the state of conventional knowledge reviewed hereinabove coupled with the guidance of the Summary section, wherein applicants' objectives were clearly manifest to use certain nucleotide sequences, expression products thereof, and synthetic peptides derived from the standard genetic translations of those sequences. Such synthetic peptides are readily used by one of ordinary skill for the purpose of detecting the presence of HIV.

As to the Office Action's discounting of the Geysen reference, applicants respectfully submit that the Office Action's own words belie the Office Action's conclusion. The Office Action recites that the "Geysen et al.

publication was a seminal publication" in the field of immunochemistry. This reference, therefore, should be viewed as reciting conventional knowledge known by those of ordinary skill in the art and applicable in the practice of the teaching of the present specification. Accordingly, contrary to the Office Action's assertion, the specification need provide no guidance to Geysen in particular because it is a reference that clearly would have been known to one of ordinary skill in the art at the time of applicants' invention. Moreover, Geysen was published in the highly visible and prestigious journal Proceedings of the National Academy of Science, which manifestly is part of the literature that records conventional knowledge known by a routineer, in this instance as of July, 1984, the publication date of the Geysen reference. See Howarth, 654 F.2d at 106-107, 210 U.S.P.Q. at 692 ("Well known text books in English are obvious research materials." Well known technical journals are also "obvious research materials." Excluded from this list, according to Howarth, would be obscure foreign-language publications, including foreign patents, particularly in the absence of providing any guidance as to the whereabouts of the required enabling information.).

Geysen et al. present a method understood by those of ordinary skill to be applicable to the analysis of the immunogenicity of fragments of any polypeptide. Indeed, Geysen et al. conclude by reciting:

> We expect that the systematic approach as outlined [in the reference], when applied to a broader spectrum of proteins, will contribute greatly to our understanding of the nature of epitopes and their interaction with the immune system.

Geysen et al., supra at 4001, second column. Whether there is any relationship between the viral capsid protein studied by Geysen et al. and the envelope gene product of the present invention is, accordingly, immaterial. Moreover, there is no evidence of record that the Geysen method would not be applicable to the HIV envelope antigen. If the Examiner is aware of such evidence, documentation thereof is requested pursuant to 37 C.F.R. §1.107(b).

The Office Action contends that Geysen et al. is deficient for not addressing the production and identification of useful conformational, as opposed to linear, epitopes. Applicants do not claim conformational epitopes, but fragments of the HIV envelope domain that function as antigens. Whether these antigens consist of linear or conformational epitopes is not material to the requirements of Section 112. The only relevant question is

whether applicants enable fragments that can function as antigens, which applicants clearly do.

Antigenic fragments of HIV proteins made by chemical synthesis, such as those identified by Cosand (U.S. Patent 4,629,783), comprise relatively short sections of amino acid sequence and are recognized by anti-HIV antibodies. Such fragments find particular use in the diagnostics area where they are capable of ready labeling and/or attachment to solid phase assay components, such as in an ELISA protocol. As noted above with respect to the discussion concerning the various Hopp references, antigenic fragments are susceptible to prediction, based upon the correlation that exists between high hydrophilicity and the presence of immunoreactivity. Geysen et al. involves the systematic synthesis of overlapping small peptides across the entire polypeptides of interest, which is clearly useful and perhaps more appropriate for the identification of small antigenic fragments. Indeed, Geysen et al. is not intended by applicants to provide information for the identification of conformational epitopes, however such information is not relevant to the practice of the invention.

In addition, the recital in Geysen et al. at page 4001, first column, that the immune response varies between individuals has no bearing on the extent to which the

present invention is enabled. At most, this information relates to the possibility that some HIV polypeptide fragments having epitopes recognized by a larger proportion of the population are more effective for some applications of the present invention than others, in that a larger proportion of the tested population would be diagnosable; in contrast those HIV polypeptide fragments having epitopes recognized by a lesser proportion of the population are less effective because a greater proportion of tested individuals may receive false negative results. Importantly, the present invention has application beyond clinical diagnostics or large scale screening of blood donations. Immunoassays are used in many situations, including studies of the reactivity of a particular region in the population at large and monitoring production of antibodies or other clinical reagents. The issue of the degree of effectiveness of a blood test, however, is appropriate for review by the Food and Drug Administration, and, ultimately, by the marketplace, but is inappropriate for review by the Patent Office. One is not required to enable a commercial product to obtain a patent.

Applicants respectfully submit that they have described and enabled various useful embodiments of the present invention, as represented by the pending claims. As

discussed hereinabove and in the December 22nd Amendment, the claims are not only enabled by the instant application, but also by the parent applications, including the '501 application. Any detail not recited therein that may be used in practicing the present invention was known by routineers at least by the October 1984 priority date, as discussed hereinabove. And, again, it is well established law that "a patent need not teach, and preferably omits, what is well known in the art" without jeopardizing its claims with respect to enablement, so long as any non-conventional information required to make and practice the invention is disclosed or readily ascertainable by one of ordinary skill. Hybritech, 802 F.2d at 1384, 231 U.S.P.Q. at 98; Howarth, supra. Such is the case here.

Accordingly, applicants respectfully request that the Section 112, first paragraph, rejection be withdrawn. Further, applicants respectfully request that the pending claims be accorded the benefit of the filing dates of the '501 and '534 applications as either one provides an enabling disclosure for the claimed invention.

Discussion Of The Indefiniteness Rejection

Claims 60-66 stand rejected under 35 U.S.C. § 112, second paragraph, because the claims are allegedly

indefinite. In particular, the Office Action stated that the term "synthetic peptide" is inadequately described in the specification, thus rendering the claims indefinite. Without acceding to that view of the Office Action, applicants have amended claims 60, 61 and 66 by including further descriptive language relating to the identity of the synthetic peptide by confirming that it is prepared by chemical synthesis. Accordingly, applicants respectfully request that the Section 112, second paragraph, rejection be withdrawn.

Discussion Of The Anticipation Rejection

Claims 60-66 stand rejected under 35 U.S.C. § 102(b) and (e) as allegedly being anticipated by Chang et al. (U.S. 4,774,175) or Cosand (U.S. Patent 4,629,783). Applicants respectfully traverse on the basis that the present application benefits from parent applications that predate the cited art, thus rendering them ineffective.

The cited references, however, disclose examples of diagnostics using particular HIV polypeptide fragments that are predicated on the earlier work of applicants. Any such HIV immunodiagnostic was first invented by applicants who, appropriately, should benefit from their pioneering work by

being granted claims that will dominate the patent positions of any such second comers.

Discussion Of The Rejection Under
Obviousness-Type Double Patenting

The Office Action repeated the rejection of claims 60-66 under the judicially created doctrine of obviousness-type double patenting in view of claims 1-22 of U.S. Patent 5,156,949. As noted by the Examiner, applicants have stated that a terminal disclaimer in compliance with 37 C.F.R. 1.321(b) with respect to the term of the '949 patent will be filed in the instant application prior to issuance of any allowed claims.

Conclusion

In view of the above amendments and remarks, the application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (312) 616-5600.

Respectfully submitted,

By _____

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In re LUCIW et al.
Serial No. 08/089,407

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